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A GENERAL APPROACH TO LIMITING NORMALITY OF THE PRODUCT-LIMIT E--ETC(U)

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by

A. J. Quinzi^{1,2} and T. M. Smith¹

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0. Introduction and Summary

In the classical theory of competing risks [cf. the excellent monograph of Birnbaum (1979)] it is assumed that (a) the risks, i.e., the random variables of interest are independent and (b) death does not result from simultaneous causes. The classical estimator for the marginal distributions of interest in the competing risks problem is that of Kaplan and Meier (1958) or generalizations thereof [cf. Peterson (1975, 1977)]. Langberg, Proschan, and Quinzi (1981) [hereafter referred to as LPQ(1981)] obtain strongly consistent estimators for the unobservable marginal distributions of interest when assumptions (a) and (b) above fail to hold. These estimators resemble those of Kaplan and Meier (1958). In Section 1, we examine the competing risks problem in the presence of dependent risks and state a number of known results. In Section 2, we establish the asymptotic normality of the LPQ(1981) estimators. Only the outline of proof is given. This preliminary report represents work currently in progress.

1. The competing risks model

Let there be a finite number of causes of death labelled $1, \dots, r$. We associate with each cause j a nonnegative random variable T_j , $j = 1, \dots, r$. The random variable T_j represents the age at death if cause j were the only cause present in the environment. The complete collection of random variables T_1, \dots, T_r is not observed. Instead, only two quantities are observed: the age at death given by $\mathcal{T} = \min(T_1, \dots, T_r)$ and the cause of death, labelled ξ , given by $I \in \mathcal{I}$ such that $\xi(\underline{T}) = I$, where \mathcal{I} represents the collection of nonempty subsets of $\{1, \dots, r\}$. Thus, $\xi(\underline{T}) = I$ if and only if $\mathcal{T} = T_i$ for each $i \in I$ and $\mathcal{T} \neq T_i$ for each $i \notin I$. When death results from exactly one of the r possible causes, as is usually assumed, then ξ is the index i for which $\mathcal{T} = T_i$. The biomedical researcher is interested in making inferences about the unobservable random variables T_1, \dots, T_r by using information from the observable quantities, namely the life length \mathcal{T} and cause of death ξ . In particular, he seeks to estimate the $2^r - 1$ survival probabilities

$$\bar{M}_J(t) = P[\min(T_j, j \in J) > t], J \in \mathcal{I}.$$

We use the following notation throughout. If T is a nonnegative random variable with distribution function F , then $\bar{F} = 1 - F$.

LPQ(1978) prove the following

Theorem 1.1. Let $\mathcal{T} = \min(T_1, \dots, T_r)$, where T_1, \dots, T_r are nonnegative random variables. Define $\bar{F}(t, I) = P(\mathcal{T} > t, \xi(\underline{T}) = I)$, $F(t, I) = P(\mathcal{T} \leq t, \xi(\underline{T}) = I)$, $I \in \mathcal{I}$, $\bar{F}(t) = \sum_{I \in \mathcal{I}} \bar{F}(t, I)$ and $F(t) = 1 - \bar{F}(t)$.

Then the following statements hold:

(i) A necessary and sufficient condition for the existence of a set of independent random variables $\{H_I, I \in \mathcal{I}\}$ which satisfy

$$P(\tau > t, \xi(\underline{T}) = I) = P[\min(H_I, I \in \mathcal{I}) > t, H_I < H_J, \text{ each } J \neq I]$$

is that the functions $F(\cdot, I), I \in \mathcal{I}$, have no common discontinuities in the interval $[0, \alpha(F))$, where $\alpha(F) = \sup \{t: 1 - F(t) > 0\}$.

(ii) The random variables $\{H_I, I \in \mathcal{I}\}$ in (i) have corresponding survival probabilities $\{\bar{G}_I(\cdot), I \in \mathcal{I}\}$, $\bar{G}_I(t) = P(H_I > t)$, which are uniquely defined on the interval $[0, \alpha(F)]$ as follows:

$$(1.1) \quad \bar{G}_I(t) = \prod_{a \leq t} [\bar{F}(a)/\bar{F}(a^-)] \cdot \exp \left[- \int_0^t dF^C(\cdot, I)/\bar{F} \right], \quad 0 \leq t \leq \alpha(F),$$

where $F^C(\cdot, I)$ is the continuous part of $F(\cdot, I)$, the product is over the discontinuities $\{a\}$ of $F(\cdot, I), I \in \mathcal{I}$, and the product over an empty set is defined as unity.

Remark 1.2. Although motivated by the competing risks model, Theorem 1.1 applies to any model where observations include (1) the time at which a particular event occurs and (2) the identity of the causes (among a finite number) which result in the occurrence of the event. For example, suppose a personnel study is undertaken to study the departure patterns of employees in a large company. The data on each employee might consist of (1) length of stay, i.e., the time from arrival to termination, and (2) the reason for termination. Here, each employee terminates (dies) for one or more of several reasons (causes).

Remark 1.3. Formula (1.1) represents each distribution in the independent collection $\{H_I, I \in \mathcal{I}\}$ as a function of the (observable) cause-specific subdistribution functions $F(\cdot, I)$, $I \in \mathcal{I}$, as well as the (observable) survival function $\bar{F}(t) = P(\mathcal{T} > t)$. It is this representation of distributions in the independent collection by observable functions which plays a key role in the estimation problem.

Let $\underline{T}_i = (T_{1i}, \dots, T_{ri})$, $i = 1, \dots, n$, represent a random sample from the joint distribution of the nonnegative random variables T_1, \dots, T_r . For each $J \in \mathcal{I}$, let $\bar{M}_J(t) = P[\min(T_j, j \in J) > t]$. For $j \in \{1, \dots, r\}$, we write $M_j(t)$ instead of $M_{\{j\}}(t)$. For each $i = 1, \dots, n$, only \mathcal{T}_i and ξ_i are observed, where $\mathcal{T}_i = \min(T_{1i}, \dots, T_{ri})$ and $\xi_i = J$ whenever $\mathcal{T}_i = T_{ji}$ for each $j \in J$ and $\mathcal{T}_i \neq T_{ji}$ for each $j \notin J$. It is important

to note that we have not made either of the two classical assumptions, namely (a) the risks, i.e., the random variables T_1, \dots, T_r are independent; and (b) death does not result from simultaneous causes, i.e., $P(T_i = T_j) = 0$ for $i \neq j$. If (a) and (b) hold, the function $\bar{M}_J(t)$ may be estimated (consistently) [cf. Peterson (1975)] by using a generalized version of the Kaplan-Meier (1958) (product-limit) estimator

$$(1.2) \quad \hat{\bar{M}}_J(t) = \prod_i [(n - i)/(n - i + 1)],$$

where the product is over the ranks i of those ordered observations $\mathcal{T}_{(i)}$ such that $\mathcal{T}_{(i)} \leq t \leq \mathcal{T}_{(n)}$ and $\mathcal{T}_{(i)}$ corresponds to a death from at

least one cause $j \in J$. If $\tau_{(n)}$ corresponds to a death from a cause $j \in J$, then $\hat{M}_j(t)$ is defined to be zero for $t > \tau_{(n)}$. Otherwise, $\hat{M}_j(t)$ is undefined for $t > \tau_{(n)}$. [In the original formulation by Kaplan and Meier (1958), $r = 2$ and T_1 corresponded to the time until death, while T_2 corresponded to the time at which a loss occurred.]

Suppose now that it is not assumed that T_1, \dots, T_r are independent. LPQ(1981) prove the following

Theorem 1.4. Let T_1, \dots, T_r be nonnegative random variables such that the functions $F(t, I) = P(\tau \leq t, \xi(\tau) = I)$, $I \in \mathcal{I}$, have no common discontinuities. Define $\mathcal{I}_I = \{J \in \mathcal{I} : J \cap I \neq \emptyset\}$. Fix $I \in \mathcal{I}$. Then for each $t \in [0, \alpha(F)]$,

$$(1.3) \quad \bar{M}_I(t) = \prod_{J \in \mathcal{I}_I} \bar{G}_J(t)$$

if and only if

$$(1.4a) \quad \bar{M}_I(a)/\bar{M}_I(a^-) = \begin{cases} \bar{F}(a)/\bar{F}(a^-), & a \in D(\mathcal{I}_I) \\ 1, & \text{otherwise;} \end{cases}$$

and

$$(1.4b) \quad P(\tau_{I'} > t \mid \tau_I = t) = P(\tau_{I'} > t \mid \tau_I > t),$$

where \bar{G}_J is given by (1.1), $D(\mathcal{I}_I)$ is the set of discontinuities of the function $F(t, \mathcal{I}_I) = P(\tau \leq t, \xi(\tau) \in \mathcal{I}_I)$, $\tau_I = \min(T_i, i \in I)$ and I' is the complement of I in $\{1, \dots, r\}$.

Remark 1.5. By finding consistent estimators for the functions \bar{G}_j in (1.3), LPQ(1981) establish that (1.4a) and (1.4b) are necessary and sufficient conditions on the joint distribution of T_1, \dots, T_r for the existence of a consistent estimator of \bar{M}_I in (1.3).

Remark 1.6. Suppose that the random variables $T_I = \min(T_i, i \in I), I \in \mathcal{I}$, have absolutely continuous distributions. Let $m_I(t)$ [respectively, $\bar{M}_I(t)$] and $m_{I|I'}(t)$ [respectively, $\bar{M}_{I|I'}(t)$] denote the density (respectively, survival) function and conditional density (respectively, conditional survival) function of T_I and $T_{I'}$ given $T_{I'} > t$. Then condition (1.4b) is equivalent to

$$m_{I|I'}(t)/\bar{M}_{I|I'}(t) = m_I(t)/\bar{M}_I(t).$$

In other words, the conditional failure rate function of T_I given $T_{I'} > t$ is equal to the (unconditional) failure rate function of T_I . Stated differently, the random variables T_I and $T_{I'}$ are independent "along the diagonal $T_I = T_{I'}$ ". This property of "diagonal independence" is of importance in the case of dependent competing risks and is presently being studied by the authors. Desu and Narula (1977) arrive at a condition similar to (1.4b) in the special case when T_1, \dots, T_r have a joint distribution which is absolutely continuous.

Suppose now that the functions $F(t, I), I \in \mathcal{I}$, have no common discontinuities. We make no assumption as to the independence of T_1, \dots, T_r . In view of (1.3), a natural estimator for \bar{M}_I is

$$(1.5) \quad \tilde{\bar{M}}_I(t) = \prod_{J \in \mathcal{I}_I} \bar{G}_{J,n}(t).$$

where $\bar{G}_{J,n}(t)$ is obtained from the right side of (1.1) by replacing

$F(\cdot, I)$ and F by their empirical counterparts

$$F_n(t, I) = n^{-1} \sum_{i=1}^n \chi_{\{\tau_i \leq t, \xi_i = I\}}$$

and

$$F_n(t) = n^{-1} \sum_{i=1}^n \chi_{\{\tau_i \leq t\}},$$

where χ_A is the indicator function of the set A . LPQ(1981) show that in

this case, (1.5) is a (strongly) consistent estimator for \bar{M}_T when (1.4a,b) hold.

Remark 1.7. If T_1, \dots, T_r are independent and $P(T_i = T_j) = 0$ for $i \neq j$, then (1.5) reduces to the usual Kaplan-Meier (1958) estimator (1.2) or a version thereof.

Remark 1.8. Suppose for a moment that we make no assumption on the underlying distribution of T_1, \dots, T_r except that the functions $F(t, I)$, $I \in \mathcal{I}$, have no common discontinuities. Let $0 \equiv \tau_{(0)} \leq \dots \leq \tau_{(n)} < \tau_{(n+1)} \equiv \infty$

denote the ordered values of times τ_1, \dots, τ_n at which deaths occur.

We do not exclude the possibility of multiple deaths at $\tau_{(j)}$. We thus obtain the (possibly degenerate) intervals $[0, \tau_{(1)}), [\tau_{(1)}, \tau_{(2)}), \dots,$

$[\tau_{(n)}, \infty)$ such that the number of deaths in any interval is exactly one.

For each interval $[\tau_{(j)}, \tau_{(j+1)})$, estimate the proportion p_j of individuals alive just after $\tau_{(j)}$ that survive the interval as follows:

let $N(t)$ = the number of individuals observed and surviving
 at t , when deaths due to cause I (but not deaths due
 to any other cause) at t itself are subtracted off;
 and $\delta_j = N(\tau_{(j)}^-) - N(\tau_{(j)})$ = the number of deaths at $\tau_{(j)}$.

Then the estimate of p_j above is

$$\hat{p}_j = [N(\tau_{(j)}^-) - \delta_j] / N(\tau_{(j)}^-).$$

Now, to estimate the probability of surviving until t if cause I were
 the only risk present in the environment, Kaplan and Meier (1958) calculate

$$(1.6) \quad \bar{M}_I^*(t) = \prod_{j=1}^k \hat{p}_j.$$

For any given set of data, formula (1.6) yields the same numerical
estimate as formula (1.5). Recall, however, that (1.5) is a consistent
 estimator of \bar{M}_I if and only if (1.4a,b) hold. Yet, even in the face of
 ignorance about the truth or falsity of (1.4a,b), we know precisely what
parameter of the underlying distribution is being estimated (consistently)
by (1.6), namely

$$(1.7) \quad \prod_{j \in \mathcal{J}_I} \bar{G}_j(t),$$

where \bar{G}_j is given by (1.1). To the authors' knowledge, this fact has
 never been pointed out.

2. The main result

In this section we outline a proof of the fact that, viewed as a process in t , the estimator (1.5) converges to a Gaussian process. As a result, we extend a result of Breslow and Crowley (1974) from the case of a continuous survival to an arbitrary survival function. For simplicity, we assume here that the distribution F of \mathcal{T} has finitely many discontinuities. The case of a countable infinity of discontinuities will be presented in a subsequent report.

We inquire into the asymptotic distribution of

$$\widetilde{M}_I(t) = \prod_{J \in \mathcal{J}_I} \bar{G}_{J,n}(t) = \prod_{J \in \mathcal{J}_I} \prod_{a \leq t} [\bar{F}_n(a)/\bar{F}_n(a^-)],$$

where the last product is over the set of observations $\{a\}$ such that $\mathcal{T}_i = a$ and $\mathcal{J}_i = J$, $i = 1, \dots, n$. Let this set $\{a\}$ of points be denoted by $D(n, J)$ and let $C(J)$ [$D(J)$] be the set of continuities (discontinuities) of the function $F(t, J)$. Then we can write

$$\begin{aligned} (2.1) \quad \sqrt{n}[\bar{G}_{n,J}(t) - \bar{G}_J(t)] &= \sqrt{n}[e^{H_{n,J}(t)} - e^{H_J(t)}] \\ &= \sqrt{n}[H_{n,J}(t) - H_J(t)] e^{H(t)} + \frac{\sqrt{n}}{2}[H_{n,J}(t) - H_J(t)]^2 e^{H^*(t)}, \end{aligned}$$

where $H_{n,J}(t) = \sum_{a \leq t} \ln [\bar{F}_n(a)/\bar{F}_n(a^-)] \chi_{D(n, J)}(a)$.

$H_J(t) = \sum_{a \leq t} \ln [\bar{F}(a)/\bar{F}(a^-)] \chi_{D(J)}(a) - \int_0^t dF^C(\cdot, J)/\bar{F}$, and the function $H^*(t)$ is between $H_{n,J}(t)$ and $H_J(t)$.

We consider first the asymptotic distribution of $\sqrt{n}[H_{n,J}(t) - H_J(t)]$.

We have

$$\sqrt{n}[H_{n,J}(t) - H_J(t)] = \sqrt{n}[A_{n,J}(t) - A_J(t)] + \sqrt{n}[B_{n,J}(t) - B_J(t)],$$

$$\text{where } A_{n,J}(t) = \sum_{a \leq t} \ln [\bar{F}_n(a)/\bar{F}_n(a^-)] \chi_{D(n,J)}^{(a)} \cdot \chi_{D(J)}^{(a)},$$

$$A_J(t) = \sum_{a \leq t} \ln [\bar{F}(a)/\bar{F}(a^-)] \chi_{D(J)}^{(a)},$$

$$B_{n,J}(t) = \sum_{a \leq t} \ln [\bar{F}_n(a)/\bar{F}_n(a^-)] \chi_{D(n,J)}^{(a)} \cdot \chi_{C(J)}^{(a)}, \text{ and}$$

$$B_J(t) = - \int_0^t dF^C(\cdot, J)/\bar{F}.$$

We can now state

Theorem 2.1. Assume that each function $F(\cdot, J)$, $J \in \mathcal{J}$, has finitely many discontinuities. Fix $J \in \mathcal{J}$ and let $0 < a_1 < \dots < a_k < \infty$ denote the discontinuities of $F(\cdot, J)$. Then the k -dimensional random vector whose i th component is

$$\sqrt{n} \sum_{j=1}^i \left\{ \ln [\bar{F}_n(a_j)/\bar{F}_n(a_j^-)] - \ln [\bar{F}(a_j)/\bar{F}(a_j^-)] \right\}$$

converges in distribution to a k -dimensional multivariate normal with mean vector $\underline{0}$ and covariance matrix $\Sigma = (\sigma_{ij})$, which can be represented thus:

$$\Sigma = \begin{bmatrix} b_1 & b_1 & b_1 & \dots & b_1 \\ b_1 & b_1+b_2 & b_1+b_2 & \dots & b_1+b_2 \\ b_1 & b_1+b_2 & b_1+b_2+b_3 & \dots & b_1+b_2+b_3 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ b_1 & b_1+b_2 & b_1+b_2+b_3 & \dots & b_1 + \dots + b_k \end{bmatrix},$$

where $b_i = [F(a_i)/\bar{F}(a_i)] - [F(a_i^-)/\bar{F}(a_i^-)]$, $i = 1, \dots, k$.

The proof of Theorem 2.1 is straightforward and is omitted.

Now define a process $Z_{J,1}(t)$ in $D = D[0, \alpha(F)]$ whose finite-dimensional distributions are multivariate normal with $EZ_{J,1}(t) = 0$ and

$$\text{Cov}[Z_{J,1}(s), Z_{J,1}(t)] = \begin{cases} \sigma_{ij} & \text{for } s \in [a_i, a_{i+1}), t \in [a_j, a_{j+1}), s \leq t \\ \sigma_{ji} & \text{for } s > t; \end{cases}$$

where σ_{ij} is the (i,j) th entry of Σ in Theorem 2.1 and $D[0, \alpha(F)]$ is

the space of functions on $[0, \alpha(F)]$ that are right-continuous and have left-hand limits. Such a process exists by Theorem 15.3 of Billingsley (1968).

Theorem 2.2. The process $\sqrt{n}[A_{n,J}(t) - A_J(t)]$ converges weakly to $Z_{J,1}(t)$ as $n \rightarrow \infty$.

Proof. Note that $\sqrt{n}[A_{n,J}(t) - A_J(t)]$

$$= \sqrt{n} \sum_{i=1}^J \left\{ \ln [\bar{F}_n(a_i)/\bar{F}_n(a_i^-)] X_{D(J,n)}(a_i) - \ln \bar{F}(a_i)/\bar{F}(a_i^-) \right\}$$

for $t \in [a_j, a_{j+1})$. For $\delta \leq \min_{1 \leq i,j \leq k} |a_i - a_j|$, it is easily seen

that $w_x^n(\delta) = \sup \min (|x_n(t) - x_n(t_1)|, |x_n(t_2) - x_n(t)|) = 0$,

where $x_n(t) = \sqrt{n}[A_{n,J}(t) - A_J(t)]$ and the supremum extends over t, t_1, t_2

such that $t_1 \leq t \leq t_2$ and $t_2 - t_1 \leq \delta$. The theorem follows from

Theorem 2.1 above and Theorem 15.4 of Billingsley (1968). ||

Breslow and Crowley (1974) show that the pair $(X_n, Y_n) \in D[0, \alpha(F)] \times D[0, \alpha(F)]$ defined by $X_n = \sqrt{n}(\bar{F}_n - \bar{F})$, $Y_n = \sqrt{n} \left[\sum_{a \leq t} X_{C(J)}(a) X_{D(J,n)}(a)/n - F^G(\cdot, J) \right]$ converges weakly to a bivariate Gaussian process (X, Y) which has mean vector zero and a covariance structure given by

$$(2.2) \quad \begin{cases} \text{Cov}(X(s), X(t)) = F(s)\bar{F}(t), \text{Cov}(Y(s), Y(t)) = F^G(s, J) [1 - F^G(t, J)] \\ \text{Cov}(Y(s), X(t)) = F^G(s, J)\bar{F}(t), \text{Cov}(X(s), Y(t)) = F^G(s, J) - F(s)F(t, J). \end{cases}$$

Thus, by Theorem 4 of Breslow and Crowley (1974), the process

$\sqrt{n}[B_{n,J}(t) - B_J(t)]$ converges weakly to the Gaussian process $Z_{J,2}(t)$ defined by

$$Z_{J,2}(t) = \int_0^t [X/\bar{F}^2] dF^C(\cdot, J) + [Y(t)/\bar{F}(t)] - \int_0^t Y d(1/\bar{F}),$$

where (X, Y) is the bivariate mean 0 Gaussian process satisfying (2.2).

Furthermore, the covariance structure of the limiting process $Z_{J,2}(t)$ can be obtained in a manner similar to that in Breslow and Crowley (1974).

Combining this result with Theorem 2.2 above, we have

Theorem 2.3. The process $\sqrt{n}[H_{n,J}(t) - H_J(t)]$ converges weakly to the Gaussian process $Z_{J,1}(t) + Z_{J,2}(t) \equiv Z_J(t)$.

Remark 2.4. The covariance structure of the limiting process in Theorem 2.3, as well as in the remaining theorems, may be obtained in a tedious but straightforward manner. The exact derivations are given in a later report.

Consider now (2.1). Since $\sqrt{n}[H_{n,J}(t) - H_J(t)]$ converges weakly, the second term in (2.1) converges to 0 in probability. Thus, we have

Theorem 2.5. The process $\sqrt{n}[G_{n,J}(t) - G_J(t)]$ converges weakly to the Gaussian process $Z_J(t) \cdot \bar{G}_J(t)$, where $Z_J(t)$ is the limiting process in Theorem 2.3.

Remark 2.6. Finally, by an application of the so-called δ -method [cf. Rao (1973)], we see that the estimator $\tilde{M}_J(t)$ given by (2.2) also converges weakly to a Gaussian process.

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